

DITRO PAN XL® (oxybutynin chloride) ER Tablets
Citizen Petition
Ortho Urology

DITRO PAN XL®

(oxybutynin chloride)

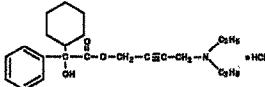
Extended Release Tablets

Prescribing Information

Description

DITRO PAN XL® (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITRO PAN XL Extended Release Tablet contains 5 mg, 10 mg, or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

Chemically, oxybutynin chloride is (±)-racemic 4-diethylamino-2-butyl phenylcyclobexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{12}H_{20}NO_2 \cdot HCl$. Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alcohols.

DITRO PAN XL also contains the following inert ingredients: cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, sodium citrate, titanium dioxide, polymethacrylate 60, sodium chloride, and butylated hydroxytoluene.

System Components and Performance

DITRO PAN XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which includes the drug and excipients, constitutes an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water penetrates through the membrane into the tablet core, causing the osmotic pressure to expand the push layer and force the drug out through the orifice. The resulting expansion pushes the suspended drug out through the orifice. The osmotic pressure is maintained by the presence of a glucose solution in the bilayer core, which provides the driving force for drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of DITRO PAN XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble stool.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit ciliary muscle, but four to five times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anticholinergic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, systematic studies have demonstrated that oxybutynin increases bladder (vesicourethral capacity), diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin thus relieves urgency and the frequency of both incontinence episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desmethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Following a single dose of DITRO PAN XL® (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; there are steady-state concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITRO PAN XL are 156% and 127%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape. Figure 1 shows the profile for R-oxybutynin.

Table 1
**Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters
 Following a Single Dose of DITRO PAN XL 10 mg (n=6)**

| Parameters (units) | R-Oxybutynin | | S-Oxybutynin | |
|-------------------------------|--------------|------------|--------------|------------|
| | Mean (ng/mL) | SD (ng/mL) | Mean (ng/mL) | SD (ng/mL) |
| T _{max} (h) | 12.7 | (5.4) | 11.8 | (5.3) |
| t _{1/2} (h) | 13.2 | (6.2) | 12.4 | (6.1) |
| AUC ₀₋₂₄ (ng·h/mL) | 18.4 | (10.3) | 34.2 | (16.9) |
| AUC ₀₋₂₄ (ng·h/mL) | 21.3 | (12.2) | 39.5 | (21.2) |

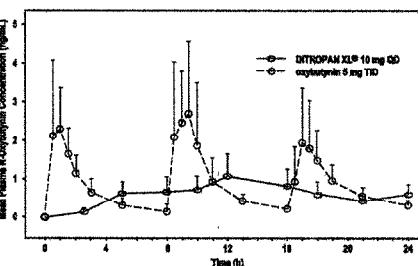


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of DITRO PAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated DITRO PAN XL dosing, with no observed drug accumulation or change in oxybutynin pharmacokinetic parameters. DITRO PAN XL plasma concentrations were reported in 103 children aged 5-19 years, with drug exposure associated with a mean total daily dose of 0.9 g, median 0.5 g. The children were on DITRO PAN XL with total daily doses ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain samples. When all available data are normalized to an equivalent of 5 mg per day DITRO PAN XL, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desmethyloxybutynin are summarized in Table 2. The plasma-time concentration profile for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 2

Mean ± SD R- and S-Oxybutynin and R- and S-Desmethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-19 Years Following Administration of 5 to 20 mg DITRO PAN XL Once Daily (n=19)

| | R-Oxybutynin | S-Oxybutynin | R-Desmethyloxybutynin | S-Desmethyloxybutynin |
|--------------------------|--------------|--------------|-----------------------|-----------------------|
| C _{max} (ng/mL) | 0.7 ± 0.4 | 1.3 ± 0.8 | 7.8 ± 3.7 | 4.2 ± 2.3 |
| T _{max} (h) | 5.0 | 5.0 | 5.0 | 5.0 |
| AUC (ng·h/mL) | 12.8 ± 7.0 | 23.7 ± 14.4 | 125.1 ± 66.7 | 73.6 ± 47.7 |

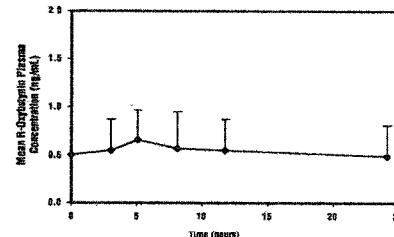


Figure 2. Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg DITRO PAN XL once daily in children aged 5-19. Plot represents all available data normalized to an equivalent of DITRO PAN XL 5 mg once daily.

Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylethoxybutynone acid, which is pharmacologically inactive, and desmethyloxybutynin, which is pharmacologically active. Following DITRO PAN XL administration, plasma concentrations of R- and S-desmethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desmethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desmethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of DITRO PAN XL are dose proportional.

Special Populations

General: The pharmacokinetics of DITRO PAN XL were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of DITRO PAN XL were evaluated in 19 children aged 5-19 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of DITRO PAN XL in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2).

Gender: There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of DITRO PAN XL.

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITRO PAN XL.

Renal Insufficiency: There is no experience with the use of DITRO PAN XL in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of DITRO PAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions: See PRECAUTIONS: Drug Interactions.

CLINICAL STUDIES

DITRO PAN XL® (oxybutynin chloride) was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (70%) and female (59%) aged 5-89 years (range, 1-78 years). Entry criteria required that patients have urge or mixed incontinence (with a primary symptom of urge or urge plus stress incontinence) and a daytime frequency of at least 8 to 10 micturitions per day. Study 1 was a fixed dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

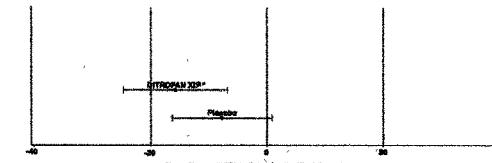
The efficacy results for the three controlled trials are presented in the following tables and figures.

Number of Urge Urinary Incontinence Episodes Per Week

| Study | n | DITRO PAN XL* | | n | Placebo |
|---------|----|---------------|---------------------------------|----|---------|
| | | Mean Baseline | Mean (SD) Change from Baseline† | | |
| Study 1 | 34 | 15.9 | -15.8 (8.9) | 16 | 20.8 |
| | | | -13.6, -2.3*† | | |

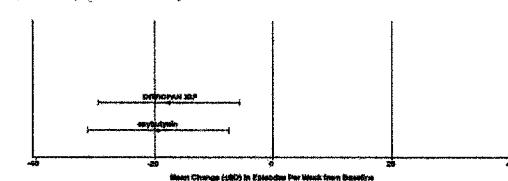
* The difference between DITRO PAN XL and placebo was statistically significant.

† Covariate adjusted mean with missing observations set to baseline values.



| Study | n | DITRO PAN XL* | | n | oxybutynin |
|---------|----|---------------|---------------------------------|----|------------|
| | | Mean Baseline | Mean (SD) Change from Baseline† | | |
| Study 2 | 53 | 27.6 | -17.5 (11.9) | 52 | -23.0 |
| | | | (-2.8, 6.5) | | |

† Covariate adjusted mean with missing observations set to baseline values.

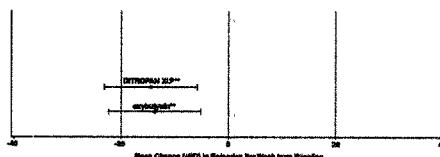


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| Number of Urge Urinary Incontinence Episodes Per Week (continued) | | | | |
|---|-----|---------------|-----|-------------|
| Study 3 | n | DITROPAN XL® | n | oxybutynin |
| Mean Baseline | 111 | 18.9 | 115 | 19.5 |
| Mean (SD) Change from Baseline† | 111 | -14.5 (8.7) | 115 | -13.8 (8.6) |
| 95% Confidence Interval for Difference | | (-3.0, 1.6)** | | |
| (DITROPAN XL® - oxybutynin) | | | | |

* The difference between DITROPAN XL® and oxybutynin fulfilled the criteria for comparable efficacy.

† Contains adjusted mean with missing observations set to baseline value



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

DITROPAN XL® is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

CONTRAINDICATIONS

DITROPAN XL® (oxybutynin chloride) is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

DITROPAN XL® is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN XL® (oxybutynin chloride) should be used with caution in patients with hepatic or renal impairment and in patients with myasthenic gravis due to the risk of symptom aggravation.

Urinary Retention

DITROPAN XL® should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders

DITROPAN XL® should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

DITROPAN XL® like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal stony.

DITROPAN XL® should be used with caution in patients who have gastro-esophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondemulcent material, caution should be used when administering DITROPAN XL® to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known structures in association with the ingestion of other drugs in nondemulcent controlled-release formulations.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) or blurred vision, patients should be advised to avoid driving or operating machinery.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that DITROPAN XL® should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush the tablet. If the medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate, the tablet shell is eliminated from the body, patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

DITROPAN XL® should be taken at approximately the same time each day.

Drug Interactions

The coadministration of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 2-fold higher when DITROPAN XL was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as amantadine agents (e.g., trizocaine and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may affect oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Concurrent ingestion of iron(II) or antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone did not significantly affect the exposure of oxybutynin or desmethyl-oxybutynin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at doses of oxybutynin chloride of 20, 60, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 23, and 60 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Salmonella typhimurium*, *Escherichia coli*, *Chlorobacillus*, *Salmonella typhimurium*, and *Salmonella typhimurium* test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL should not be given to pregnant women unless, in the judgment of the physician, the potential clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN XL is administered to a nursing woman.

Pediatric Use

The safety and efficacy of DITROPAN XL were studied in 60 children in a 24-week, open-label trial. Patients were aged 6-15 years, all had urge urinary incontinence in conjunction with detrusor instability (e.g., spina bifida), all used clean intermittent catheterization, and all were currently using oxybutynin chloride. Study results demonstrated that treatment with DITROPAN XL 5 to 20 mg/day was associated with an increase from baseline in mean urine volume after morning awakening from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 169 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H₂O to 33 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 60% to 28%.

DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (See DOSAGE AND ADMINISTRATION).

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations: Geriatric).

ADVERSE REACTIONS

Adverse Events with DITROPAN XL

The safety and efficacy of DITROPAN XL® (oxybutynin chloride) was evaluated in a total of 580 participants who received DITROPAN XL in 4 clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Three of these studies allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from these three controlled clinical studies and one open label study in the first column of Table 3 below. Adverse events from two additional fixed dose, active controlled, 12 week treatment duration studies are provided in Table 3. Adverse events from the 12 week treatment duration study with DITROPAN XL 10 mg/day, are also listed in Table 3 (second column). The adverse events are reported regardless of causality.

Table 3
 Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using DITROPAN XL (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10mg/day) Studies

| Body System | Adverse Event | DITROPAN XL 5-30 mg/day (n=429) | DITROPAN XL 10 mg/day (n=76) |
|----------------|-------------------------|---------------------------------|------------------------------|
| General | headache | 10 | 6 |
| | asthma | 7 | 3 |
| | pain | 7 | 4 |
| Digestive | dry mouth | 61 | 28 |
| | constipation | 13 | 7 |
| | diarrhea | 9 | 7 |
| | nausea | 9 | 2 |
| | dry eyes | 7 | 5 |
| Nervous | somnolence | 12 | 2 |
| | dizziness | 6 | 4 |
| Respiratory | rhinitis | 6 | 2 |
| Special Senses | blurred vision | 8 | 1 |
| | dry eyes | 6 | 3 |
| Urogenital | urinary tract infection | 5 | 5 |

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The overall incidence rate for all adverse events was 6.8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most common adverse event causing early discontinuation of study medication was nausea (1.8%), while discontinuation due to dry mouth was 0.7%.

In addition, the following adverse events were reported by 2% to < 5% of the 429 patients who received 5-30 mg/day of DITROPAN XL in the 4 efficacy and safety studies: General: abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome, cardiovascular hypertension, palpitation, vasodilation; Ocular: tinnitus, gastritis, epigastric pain; Musculoskeletal: arthritis; Nervous: insomnia, nervousness, confusion; Respiratory: upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; Skin: dry skin, rash, Urogenital: impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional adverse events reported from worldwide postmarketing experience with DITROPAN XL include peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, constipation, and impotence.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

OVERDOSE

The continuous release of oxybutynin from DITROPAN XL® (oxybutynin chloride) should be considered in the treatment of overdose. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdose of oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, tachycardia, hypertension, cardiac arrhythmia, vomiting, and urinary retention.

Input of 100 mg oxybutynin chloride in capsules to a healthy 10-year-old boy has been reported in a 13-year-old boy who experienced memory loss, and a 24-year-old woman who developed stupor followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retching at urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

DITROPAN XL® (oxybutynin chloride) must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL® may be administered with or without food.

Adults: The recommended starting dose of DITROPAN XL is 5 or 10 mg once daily at approximately the same time each day. Dose may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day).

In general, dosage adjustment may proceed in approximately weekly intervals.

Children: patients aged 6 years of age and older: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

DITROPAN XL® (oxybutynin chloride) Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (dark), and 15 mg (gray) and are supplied with "5 XL", "10 XL", or "15 XL". DITROPAN XL Extended Release Tablets are supplied in bottles of 100 tablets.

| | | |
|-------|------------------|--------------------|
| 5 mg | 100 count bottle | NDC 1731-5-3800-1 |
| 10 mg | 100 count bottle | NDC 1731-10-3801-1 |
| 15 mg | 100 count bottle | NDC 1731-15-3802-1 |

Storage

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature). Protect from moisture and humidity.

Rx Only

For more information call 1-888-385-1232 or visit www.DITROPANXL.com

Manufactured by ALZA Corporation, Mountain View, CA 94043



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